

OTS: 60-11,473

JPRS: 2465

6 April 1960

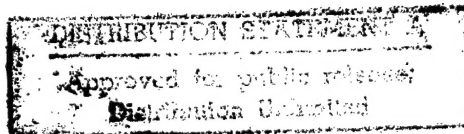
THE EFFECT OF ANTICHOLINERGIC SUBSTANCES ON GASTRIC
SECRETION IN DOGS

- CZECHOSLOVAKIA -

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THE EFFECT OF ANTICHOLINERGIC SUBSTANCES ON GASTRIC
SECRETION IN DOGS

III. Effect on Gastric Secretion Stimulated
by Administering Food

[This is a translation of an article written by J. Metys and Z. Votava, of the Research Institute of Pharmacology and Biochemistry, Prague, Dr. Engr O. Nemecek, director, in Casopis lekaru ceskych, Vol XCVIII, No 47, 20 November 1959, Prague.]

In our previous communications we investigated the effect of a number of anticholinergic substances: α -thiospasmine and Hydroxythiospasmine, two substances prepared in the VUFB [Vyzkumny ustav pro farmacii a biochemii; Research Institute of Pharmacology and Biochemistry], atropine, and foreign-made oxyphenonium (Antrenyl) and methantheline (Banthine), the substances producing a sympathomimetic effect; and the spasmolytics of papaverine both influencing gastric secretions stimulated by administering histamine, and we also investigated hypoglycaemia caused by insulin (Metys, Votava, 1959; Metys and others, 1959). This communication contains the results of comparing the effect of the above substances on the secretory response of the Pavlov pouch after the administration of food. Gastric secretion stimulated by histamine probably affected mainly the parietal cells of the gastric mucous membrane, and the parasympathetic nervous system played the major role in the secretion stimulated by hypoglycaemia; on the other hand, secretion stimulated by food is a more complicated problem (Gregory, 1956). It seems that the application of this type of stimulation brings us more closely to the natural physiological conditions.

Methodology of the Experiments

In our experiments we used five dogs with a Pavlov pouch (male dogs weighing 16, 17, 19.5, 24 and 25 kilograms). In two dogs the pouch operation was performed according to Soloviev's method (1952); the rest were operated on according to the method of Neuwelt and others

(1940). We introduced a "Spofacrylic" or "Dentacrylic" cannula into the cardiac orifice of the pouch. For technical reasons, the standard diet requirements for the experimental animals were only partially observed.

The dogs were deprived of food 16 to 18 hours before the experiment; they could drink water ad libitum. Experiments were performed in a quiet room during the early morning hours two or three times a week; and one of them always served as a control. Gastric secretion was stimulated by administering cut boiled horse meat in a constant volume for each dog. Secretion was sampled from the first animal every thirty minutes, and from the rest every twenty minutes, this arrangement enabling us to record more precisely the changes in the secretory activity. In most cases we observed the gastric secretion during the four hours following the administration of food. As previously, we investigated the pulse rate, and the dilatation and reaction of the pupil. As far as details of gastric juice are concerned, we refer to the previous study (Metys and others, 1959). A separate communication will be devoted to the peptic activity of the secernent juice.

The tested substances were administered to all experimental animals subcutaneously 30 minutes after they were fed; a physiological solution was injected in the control experiments. For the purpose of orientation one of the dogs was given the tested substances not only by parenteral administration but also orally in a wafer 30 minutes before feeding; glucose was administered orally during the control experiments. Eight to 15 control experiments were performed in each animal. We used them as a basis for calculating the average value for each animal of the concentration of free HCL, the volume of the secernent gastric juice within the reliability limit for $p = 0.95$, and the limit of insignificance in administering the tested substances with regard to the difference between the control average and the value acquired during the single experiments. We then compared the gastric secretion caused by the tested substances with the average values.

Each tested substance was administered to four of the five experimental animals in two different doses, and only by way of an exception did we administer an additional dose of the tested substance or repeat the same dose. We administered most of the tested substances in only one dose to one of the experimental animals.

Results

Control Experiments

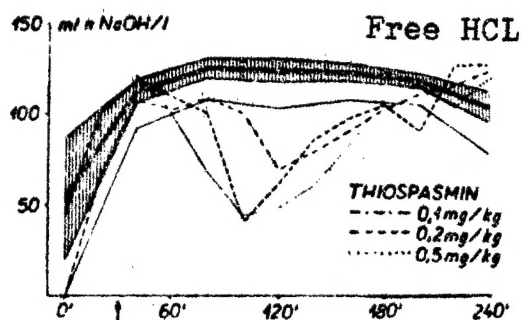
The basal secretion from the pouch was mucous and viscous. The appearance of the secreted gastric juice had changed already in its first portion (20 to 30 minutes after the administration of food); secretion from the pouch was aqueous, ranging from a slightly turbid to a clear appearance; its volume, concentration of free HCL, and acidity usually increased simultaneously. Maximum values of the individual components were reached 40 to 80 minutes after the administration of food; in most cases acidity reached its peak later than the maximum volume of the secreted juice. The volume of the secreted juice dropped to about 30 to 50 percent of its maximum value at the end of the fourth hour of the experiment and did not drop below 80 percent by the end of the experiment.

The pulse rate and the dilatation and reaction of the pupil did not change much during the control experiment.

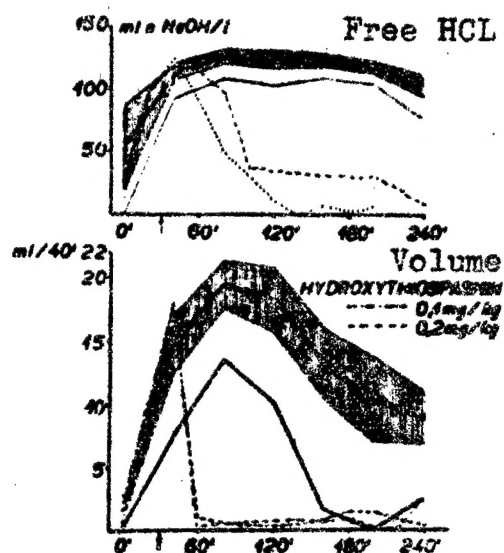
Administration of the Tested Substances

Gastric Secretion All tested anticholinergic substances (atropine, Thiopasmine, Hydroxythiopasmine, oxyphenonium, methantheline) showed a clearly inhibitory effect especially on the volume of the secreted gastric juice, and also on the concentration of free HCL, but only after a substantial drop in the volume of the juice.

Thiopasmine showed a moderate, but significant inhibitory effect on the volume of the secreted juice during 40 to 60 minutes after administering only 0.05 milligram/kilogram; acidity dropped only slightly below the limit of significance. The inhibitory effect on gastric secretion rose only moderately after the dose was increased; acidity dropped sooner and was more pronounced, but there was no substantial difference in the return to the normal and usually higher values between doses of 0.1, 0.2, and 0.5 milligram/kilogram. The acidity of the juice did not drop to the zero value even after administering 0.5 milligram/kilogram of Thiopasmine (Graph 1). There was a very substantial drop in the volume of the secreted juice immediately after resorption (after 5 to 10 minutes); the volume values returned to the control values at a slower rate than the acidity of the juice; but even after the highest dose the secretion response returned to normal values during the four hours of the experiment.



Graph 1. Effect of Thiospasmine on the concentration of free HCL in gastric juice (Dog Kazan). The y-axis shows ml of consumed n NaOH per liter, the x-axis the time in minutes. 0 indicates the administration of food; the arrow indicates the point at which Thiospasmine was administered subcutaneously. The control variable values (9 experiments) are indicated by the solid line; the hatched space indicates their limits of reliability for $p=0.95$. The thinner solid line, parallel to the lower limit of the variable values, indicates the limit of significance of the individual doses of the tested substance. Departures below this limit are statistically important.



Graph 2. Effect of Hydroxythiospasmine on gastric secretion (Dog Kazan). The upper graph indicates changes in the concentration of free HCL; the lower shows changes in the volume of secreted juice following subcutaneous administration of Hydroxythiospasmine. The y-axis in the lower graph indicates the volume of juice in ml per 40 minutes. Other indicators are the same as in Graph 1.

Hydroxythiospasmine showed a very intensive and relatively long-lasting inhibitory effect on gastric secretion. A dose of only 0.025 milligram/kilogram reduced the volume of the secretory juice appreciably for 100 to 120 minutes, and acidity dropped below 25 percent of its average value. A dose of 0.05 milligram/kilogram reduced the volume substantially, and it reduced the concentration to the zero value. The return of the acidity was observed at the end of the third hour of the experiment when a dose of 0.025 milligram/kilogram was applied; when 0.05 milligram/kilogram were used the inhibitory effect lasted practically until the end of the experiment. When 0.1 milligram/kilogram was applied the drop in the volume of juice was very sharp, statistically important, and lasted until the end of the experiment. Concentration of free HCL dropped in most cases 30 to 40 minutes after the volume of juice. A weak secretory response took place after administering food at the end of one experiment. A dose of 0.2 milligram/kilogram of Hydroxythiospasmine produced a total inhibitory effect, and there were no practical differences after administering 0.5 milligram/kilogram (Graph 2). There was no secretory response even when food was administered four hours after the injection of the tested substance.

Administration of atropine produced effects in the change of the secretory response similar to those following the injection of Hydroxythiospasmine. There was practically no difference after administering a 0.025 milligram/kilogram dose. When 0.05 milligram/kilogram of atropine was applied, the inhibitory effect was somewhat more protracted than when Hydroxythiospasmine was injected, but acidity did not drop to the zero value. Both values returned, or were returning, to the normal values during the fourth hour of the experiment. Similarly, the drop in the volume was very sharp after administering 0.1 milligram/kilogram of atropine, but its duration was a little more protracted; the concentration of free HCL declined steeply 30 to 40 minutes later to the zero value. The secretion and the drop in the concentration of free HCL to zero value were practically arrested after administering 0.2 milligram/kilogram of atropine (Graph 3). A secretory response was observed in one case after administering food following the experiment; there was no response in another experiment.

Methantheline first inhibited the volume of the secretory juice and later the concentration of free HCL, but its effect was relatively short-lived. A dose of 0.05 milligram/kilogram produced an inhibitory effect on the

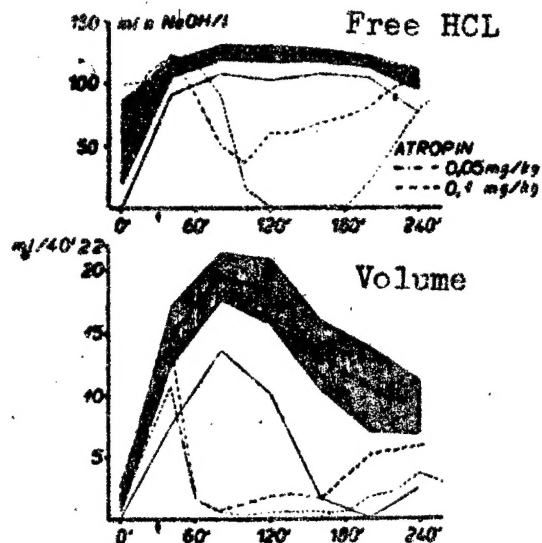
volume of the secretory juice for a period of 60 minutes; it rose proportionally with the gradually increased doses and lasted 80 to 120 minutes when the dose reached 0.2 milligram/kilogram. Practically all experiments with doses between 0.1 and 0.2 milligram/kilogram produced a drop in the concentration of free HCL close to the values of about 50 percent of the average concentration, or even below that level. The secretory response returned to the control or higher values during the final stage of the experiments (Graph 4).

An injection of 0.025 milligram/kilogram of oxyphenonium caused a sharp drop in the volume of juice as well as in the concentration of free HCL, and both values returned to the control values only at the end of the fourth hour of the experiment. Achlorhydria was reached only after a dose of 0.05 milligram/kilogram of oxyphenonium, and a practically total inhibition until the end of the experiment was caused by a dose of 0.1 milligram/kilogram of oxyphenonium.

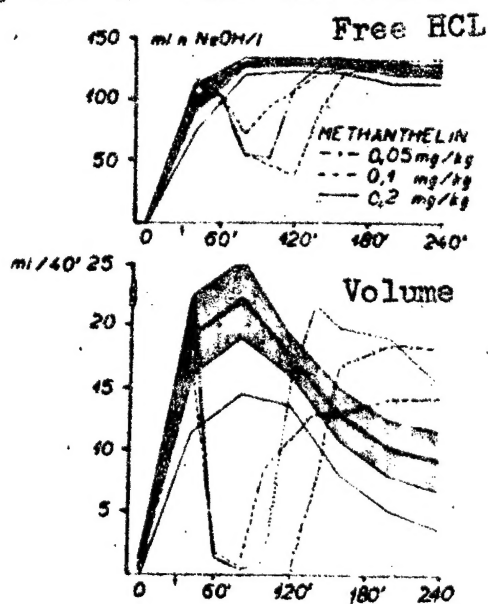
A number of experiments with the less effective tested anticholinergic substances (Thiospasmine, methantheline) brought not only a return of the secretory response to its normal values, but also a significant rise in gastric secretion provided that doses were administered in such volumes that there was a discernible inhibitory effect which, however, faded away in approximately the middle or during the third part of the experiment.

There was nothing characteristic in the effect of ephedrine on gastric secretion. Administration of 2.5 milligrams/kilogram did not substantially change the volume of the secretory juice; in two or three experiments there was a moderate, though statistically significant, drop in the concentration of free HCL. The secretory response did not change in one of the seven experiments in which 5 milligrams/kilogram of ephedrine were administered; the rest of these experiments showed a drop in the volume of the secretory juice which was, however, short-lived in most of the cases. Concentration of free HCL dropped narrowly below the limit of significance during three experiments.

A dose of 5 milligrams/kilogram of papaverine affected neither the volume nor the concentration of free HCL in gastric juice. Higher papaverine doses unfavorably affected the over-all condition of the animals.



Graph 3. Effect of atropine on gastric secretion (Dog Kazan). Same indicators as in Graph 2.



Graph 4. Effect of methantheline on gastric secretion (Dog Kazan). Same indicators as in Graph 2. Average values from 8 experiments.

Pulse Rate Thiopasmine doses affected the pulse rate in a significant way only after they reached 0.2 and 0.5 milligram/kilogram. The effect, however, was of short duration. Atropine and Hydroxythiopasmine affected the pulse rate in approximately the same way. Doses of 0.025 milligram/kilogram produced a moderate acceleration; a more pronounced acceleration was caused by 0.05 milligram/kilogram, and 0.1 milligram/kilogram and higher doses caused the greatest acceleration. Methantheline doses of 0.05 milligram/kilogram caused a moderate acceleration of the pulse rate; a more significant acceleration was caused by doses of 0.1 milligram/kilogram or higher; tachycardia was relatively short-lived. All administered doses of oxyphenonium accelerated the pulse rate significantly. Ephetone produced a rather moderate bradycardia, and papaverine did not change the pulse rate.

Effects on the Pupil Results were identical with those published previously (Metys and others, 1959). Here we mention only the following observation: a Thiopasmine dose of 0.5 milligram/kilogram affected the dilatation of the pupil in a medium to substantial way; the light reaction was short. Atropine and Hydroxythiopasmine doses of 0.2 milligram/kilogram and higher produced a high degree of mydriasis and the light reaction until the end of the experiment. Methantheline doses of 0.05 milligram/kilogram did not affect the pupil; doses of 0.2 milligram/kilogram caused a medium to substantial dilatation of the pupil, and its light reaction was unsure and short.

Oral Administration of Anticholinergic Substances

Control experiments (7) in which glucose was administered in wafers per os were not different from other control experiments with the same animal. A pronounced inhibitory effect on gastric secretion during almost the entire experiment was produced by the following doses: 10 milligrams/kilogram of Thiopasmine, 1 and 2.5 milligrams/kilogram of Hydroxythiopasmine, 5 milligrams/kilogram of methantheline; our results with atropine were less homogeneous. An inhibitory effect was produced by doses of 0.05 to 0.25 milligram/kilogram.

The ratio between parenteral and oral doses of approximately the same effect were as follows:

Thiospasmine	1:20-50
Hydroxythiospasmine	1:40-100
methantheline	1: < 25
atropine	1:2-10

The inhibitory effect of Thiospasmine and methantheline was perceived in the ascending part of the secretory response in the first 40 minutes following the administration of food; the inhibitory effect of Hydroxythiospasmine developed only after the first 40-minute interval, evidently because of a slower Hydroxythiospasmine resorption from the digestive tract.

The parenteral administration of the tested substances affected gastric secretion significantly through doses which also produced undesirable effects - effects on the pulse rate and the pupil. Oral administration of anticholinergic substances affected the pulse rate, as well as the dilatation and reaction of the pupil, relatively little. For instance, 10 milligram/kilograms of Thiospasmine or 1 to 2.5 milligram/kilograms of Hydroxythiospasmine produced no effect despite the fact that, as mentioned above, they had a pronounced inhibitory effect on gastric secretion almost during the whole experimental period. A methantheline dose of 5 milligram/kilograms, with a similar inhibitory effect on gastric secretion, caused a moderate, not a maximum, acceleration of the pulse rate. Similarly, only the highest atropine dose - 0.25 milligram/kilogram - affected the pulse rate; however, these latter results are less homogeneous.

Discussion

The above results prove that among the substances prepared in the VUFB, Hydroxythiospasmine was the most effective during parenteral administration; it can be compared with atropine in its effect on gastric secretion, as well as on the pulse rate and the pupil. The effect of atropine and Hydroxythiospasmine was intensive and protracted. The following difference between the two substances was observed; the drop in the acidity of the juice was sharper, but shorter, after the atropine injection; administration of Hydroxythiospasmine had a slower and more protracted effect.

Thiospasmine had a qualitatively different effect on gastric secretion. A parenteral administration caused a lower and shorter effect, and acidity of the juice did not drop to the zero value even after a dose of 0.5 milligram/kilogram. In addition, the undesirable effects were less pronounced and their duration was shorter.

Results in this communication correspond very well to the previous findings (Votava and others, 1957). The introduction of the hydroxyl group into the Thiospasmine molecule - i.e. the preparation of Hydroxythiospasmine - increased the spasmolytic effect in the pharmacological tests on the isolated organs of anesthetized and non-anesthetized animals while toxicity increased roughly three times, but there was a substantial increase in the anticholinergic properties of Hydroxythiospasmine: Hydroxythiospasmine has approximately the same vagolytic effect, and the same effect on lacrimation stimulated by mecholyl and on salivation stimulated by pilocarpine; Thiospasmine was four to ten times less effective in these tests.

The present results show Hydroxythiospasmine as an effective anticholinergic substance with all advantages and disadvantages of the substances of this group. On the other hand, the anticholinergic influence of Thiospasmine is probably responsible only partly for its effect, and there is another factor, probably a direct effect on muscles, in its spasmolytic effect; therefore, Thiospasmine would be closer to Trasentine H not only in its structure but also in its effects.

Xyphenonium seems to be the most effective anticholinergic substance of the tested substances administered parenterally; it also had the strongest effect on the pulse rate. Our results of its effect on gastric secretion were not different from those previously published (Barrett and others, 1953). The effect of oxyphenonium on the pupil is less pronounced, in accord with the findings of Plummer and others (1953), and with our previous results (Metys and others, 1959). Atropine and Hydroxythiospasmine are less effective than oxyphenonium, and methantheline and Thiospasmine are even less effective. The effect of methantheline and Thiospasmine is relatively short-lived; methantheline causes a sharper drop in the volume and especially in the acidity of the secreted juice, but its effect on the pulse rate and especially on the pupil is more pronounced than that of Thiospasmine. Interesting also is the increase in gastric secretion after the fading away of the effect of Thiospasmine and methantheline during some of the experiments. In comparing the effect of the tested substances we were able to determine the fact that their place was always the same with regard to all experimental animals, and that it corresponded to the conditions determined during the stimulation

of gastric secretion by hypoglycaemia (Metys and others, 1959), despite some differences in the sensitivity of animals to the anticholinergic substances, and despite slight differences in the reaction of the same animal to repeated administration of the same tested substance.

As in the case of gastric secretion stimulated by hypoglycaemia, the tested anticholinergic substances affect mainly the volume of the secreted gastric juice; acidity of the juice is reduced to the zero value only after its volume is reduced substantially and the administered doses are sufficiently large. A substance having obvious cholinergic properties, when administered parenterally, can affect gastric secretion significantly, but its doses are large enough to also produce undesirable effects on the pulse rate and the pupil. We cannot, therefore, speak of a selective inhibitory effect of anticholinergic substances on gastric secretion; these substances block the cholinergic neurohumoral mechanism of the whole organism. It seems that the effect on the pupil is a more exclusive one. Here, we found different conditions during the oral administration, but so far only in the orientation experiments. The undesirable effects were smaller as compared with the intensive inhibitory effect on gastric secretion.

In concluding this article we would like to emphasize that the reported results are a contribution to the problem concerning the mechanism of the effect of the above substances, but they are, despite some interesting features, only experimental in nature and cannot be applied uncritically to man. Only careful clinical experiments, not yet completed, will decide whether Thiospasmine and Hydroxythiospasmine could be applied in clinical practice.

Special thanks go to Engr Z. Roth for his statistical evaluation.

Summary

1. The authors investigated the effects of several anticholinergic substances - atropine, Thiospasmine, Hydroxythiospasmine, oxyphenonium, methantheline - as well as of ephedrine and papaverine on gastric secretion after administration of food to dogs with a Pavlov pouch.

2. The anticholinergic substances tested inhibited mainly the amount of juice secreted, and only when the volume was

considerably reduced did they reduce also the concentration of free HCL. After the administration of Thiospasmine, achlorhydria did not develop, not even after a dose of 0.5 milligram/kilogram.

3. The strongest inhibitory effect on gastric secretion was produced by oxyphenonium; atropine and Hydroxythiospasmine were less effective, their effect being approximately identical; methantheline and Thiospasmine produced the weakest and a relatively short-lived effect.

4. Undesirable effects of the tested anticholinergic substances administered parenterally generally ran parallel to the intensity of the inhibitory effect on gastric secretion. Such effects were relatively less pronounced in relation to the intensity of their inhibitory effect on gastric secretion during the orientation experiments when they were administered orally.

5. Ephedrine did not affect gastric secretion in a characteristic way; papaverine had no effect on the secretion of gastric juice.

END